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Remington: The Science and Practice of Pharmacy

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CHAPTER 38

Preformulation

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PREFORMULATION CHALLENGES

Bridging Discovery and Development

Preformulation activities range from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage forms. Critical information provided during preformulation can enhance the rapid and successful introduction of new therapeutic entities for humans. For example, the selection of compounds that have physical properties favorable for oral absorption early in discovery can facilitate the rapid progress of these compounds at all stages of development. Similarly, the adaptation of technologies that permit the rapid selection of a salt that is best suited for development can facilitate the manufacturing of the final market-image dosage form. The broad range of activities in preformulation requires a continuing dialog between scientists in many different disciplines, as shown in Figure 38-1.

Discovery to Development

The introduction of mechanism-based mass screening of small molecules in the late 1980s ushered in a new discovery era. Previously, animal tissue and whole animal screens had been used to find new chemical entities (NCE) that had therapeutic potential. Although the throughput was low, the final candidates for development had proven activity in animals. Today, recombinant enzymes and receptors are used in high-throughput *in vitro* screens that can evaluate quickly the hundreds of thousands of compounds that are found in chemical libraries. Active compounds (mass screen hits) then are evaluated, and some are used as the basis for further synthetic efforts. Because synthesis of new compounds can become rate limiting, combinatorial methods have been developed to synthesize rapidly new compounds using automated technologies. Today, even newer technologies are being used to increase speed and reduce material consumption. This is the attraction for using nanotechnologies in screening, synthesis, purification, and analysis.

All of these innovative changes have had a cascading impact on development. Unprecedented *in vitro* activity and specificity can now be found using recombinant proteins and automated mass screening, but aqueous solubility problems are masked by dimethyl sulfoxide, a universal solvent that is used to dissolve chemical libraries for testing. As a result, although many initially promising NCEs are extremely potent in the *in vitro* enzyme assays, they are inactive *in vivo* because of their unfavorable solubility and dissolution characteristics in the aqueous media of the body. This provides a demanding challenge for the preformulation scientist because, with mechanism-based therapy, testing in humans is often the only means of evaluating the efficacy of a new therapeutic strategy.

Integrating Discovery and Development

If unfavorable physical properties can be minimized before extensive *in vitro* optimization occurs, it may be possible to reduce the time required to discover *active and absorbable* NCEs that are poised for rapid development. Integrating discovery and development, however, will require that preformulation scientists develop a greater understanding of the molecular mechanisms of unfavorable physical properties such as aqueous insolubility. This knowledge then will provide a rational basis for making structural modifications that can enhance physical properties while *in vitro* activity also is being optimized. Figure 38-2 shows the potential time delay in discovering an orally active NCE when only activity is optimized, compared to the potential time savings when both activity and aqueous solubility are balanced for oral absorption.

Assume that a company has a chemical library of thousands of compounds that it wants to screen for a particular therapeutic target. It has isolated the appropriate receptor (protein) and has developed a high-throughput mass screen for its *in vitro* activity. In addition, for every compound that is screened for activity, it can determine aqueous solubility using a high-throughput method. Figure 38-2 shows a plot of activity versus solubility for the screened compounds. For simplicity, an ellipse is used to show regions that are possible for this hypothetical receptor. The inverse relationship shown by the ellipse, with the major axis decreasing from left to right, is based on anecdotal observations that compounds that have high *in vitro* activity often have poor aqueous solubility. A molecular explanation for why such a relationship might exist is given in the section *Aqueous Insolubility*, page 716. The two-phase discovery of an orally active NCE will now be discussed.

During Discovery Phase A, the company used *in vitro* activity as its only criterion for discovering the best compound to develop. Point 0 on the ellipse shows a compound that was chosen for further synthetic optimization on the basis of mass screening. This compound had the highest in vitro activity. During optimization, mass screens were used to provide feedback to direct the synthesis of more active analogs. Compound 1 was the most active NCE the discovery team found. However, this compound is also the most insoluble NCE on the ellipse. Enthusiasm for the compound diminished when *in vivo* animal testing showed inadequate blood levels. A lack of absorption due to poor aqueous solubility was suspected as the cause (other studies had shown that metabolism and permeability did not account for the low blood levels).

During Discovery Phase B, aqueous solubility and *in vitro* activity were optimized simultaneously. The NCE shown at

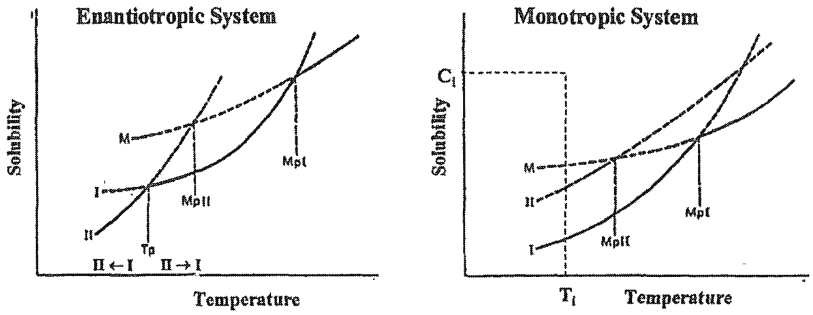


Figure 38-10. Thermal stability of polymorphic systems.[13,14]

stable form at a given temperature will have lower solubility at that temperature.

Enantiotropicity exists only when the transition point is below the melting point of Form I (see Fig 38-10). However, if a transition point is not found below the melting point of Form I, it does not mean that the system is monotropic.[14] The transition point, for example, could be below the lowest temperature studied.

For monotropic systems, interconversion is always from the metastable Form II to Form I. The solubility curve of Form II is always above that of Form I, and a transition point does not exist because a crystal cannot be heated above its melting point (see Fig 38-10). Oswald's Law of Stages dictates that if a system is supersaturated with respect to Form II at concentration C_i and T_i, the metastable Phase II will be the first solid phase that appears.[16] As Form II continues to crystallize, the supersaturation is reduced until it reaches its solubility. At this point, although there is no longer a driving force to crystallize more Form II, the solution continues to be supersaturated with respect to Form I. Thus, crystallization of Form I occurs at the expense of the dissolution of Form II.

Polymorphic Solubility: Difference Between Equilibrium and Dissolution-Based Solubility—Assume Polymorphs I and II are possible for an NCE. Oswald's Law of Stages tells us that a supersaturated solution will first crystallize out as Form II and then ultimately Form I. Thus, the thermodynamic equilibrium solubility will be limited by the solubility of Form I. However, because the rate of nucleation of II and I is a function of a wide variety of variables, equilibrium solubility is not an especially useful parameter in estimating the impact of a polymorph form on the absorption of drug from a dosage form. A dissolution-based solubility definition is more useful in this regard. How might such a solubility be defined?

Because the metastable state Form II has a faster dissolution rate, $dA/dt_{II} > dA/dt_{I}$, where it is assumed that dissolution is carried out under sink conditions of Equation 17. Because $dA/dt = k_d S_a C_S$, we can conclude that $C_S(II) > C_S(I)$ if we assume that S_a and k_d are the same for both polymorphs. Thus, Equation 17 provides a working definition for the solubility differences between Polymorph II and Polymorph I, and it provides a method for measuring them from dissolution experiments. More precisely, it provides the solubility at the surface of the API, which is the solubility that is most relevant for dissolution (see the section *Reactive Media 1*, page 706).

Polymorph Characterization Techniques—At a given temperature, a fluid-phase transformation can cause a metastable polymorph to change into a more stable, less soluble polymorph. Using a hot-stage microscope, fluid-phase transformations as a function of temperature can be observed.[14] As the temperature is varied, the more soluble polymorph dissolves and the less soluble one grows. If a temperature can be found at which both polymorphs have the same solubility, then the system is enantiotropic, and the temperature is the transition point, T_p. Plots similar to Figure 38-10 can be constructed qualitatively in which the intersection is the measured transition point. These plots are important because they tell which form is most stable at low temperatures, and whether the system is enantiotropic.

Differential scanning calorimetry (DSC) is another characterization tool that is commonly used. It can measure heat changes that occur when a solid undergoes phase transitions. Melting of a solid into a fluid, for example, requires an influx of heat into the crystal. Two techniques are useful for detecting polymorphic systems using DSC: scanning-rate variation and temperature cycling.

Scanning-rate variation has been shown to detect some reversible polymorphic systems. In Figure 38-11, crystallization of the more stable polymorph shows up as exothermic depressions as the scanning-rate increases.[17] Hot-stage microscopy can be used to confirm these thermal changes.

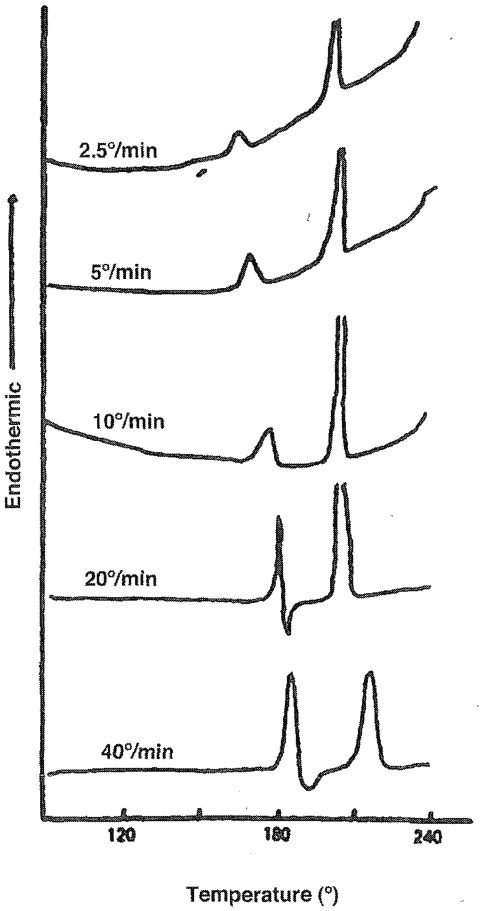


Figure 38-11. Detection of polymorphs by varying the DSC scanning rate.[17]

Temperature cycling using DSC also can be used to study the relative interconvertability of crystalline forms. A loss of the metastable, lower melting point polymorph of metoclopramide base was found after heating, cooling, and then reheating.[18] The more stable polymorph can often be observed as exotherms due to crystallization after heat–cool cycles.[19] In addition, storage of a metastable polymorph below the melting point of either polymorph can result in the formation of the more stable polymorph. For gepirone hydrochloride, this occurred after a heat treatment of 3 hours at 150°.[17]

Powder X-ray diffraction is the most powerful method for detecting polymorphs. Because different polymorphs have different crystal structures, the packing patterns of their atoms are different. Powder X-ray diffraction detects these packing differences as differences in diffraction patterns. Comparisons of diffraction scans between different polymorphs show characteristic differences that can be used for identification (fingerprinting) purposes.

Single-crystal X-ray diffraction is the most definitive characterization tool because the exact relative locations of atoms in the molecular crystal can be determined. However, most often, high-quality crystals for this type of analysis are not available from the bulk API (especially if the material was milled). Recrystallization of suitable crystals from saturated solutions may be possible. If the single-crystal X-ray diffraction problem can be solved, programs are now available that can convert single-crystal diffraction data to a powder X-ray diffraction pattern. This is necessary to ensure that the recrystallization process has not grown a new polymorph.

Solid-state nuclear magnetic resonance (NMR) is also a powerful technique for studying polymorphic systems. In this technique, a powder sample must be rotated at a special angle (the *magic angle*) with respect to the magnetic field so that preferential orientations of the powder particles are averaged. Microcalorimetry also has been used to characterize the thermodynamic properties of different polymorphs. Finally, diffuse reflectance infrared Fourier-transform spectroscopy recently has been used to quantify binary mixtures of polymorphs using the partial least-squares method for spectral analysis.[20]

Metastable Polymorph Formation—Exploring the potential that a given salt has for polymorph formation is a very important aspect of salt selection. It is important that the choice of the final molecular form be based on as much information as possible. Other factors being equal, a molecular entity that forms polymorphs is generally not as desirable as one that does not, because of the potential interconversion of polymorphs and a change in an API's dissolution. This could cause consistency problems both in the API and in the dosage forms. Special techniques are used to attempt to synthesize metastable polymorphs. Preparation of metastable polymorphs requires:

1. Supersaturating conditions for the metastable form, ${}_{\mathrm{II}}A$.
2. Crystallization of the metastable state before the stable polymorph forms.
3. Stable conditions for the metastable polymorph so that conversion to the stable ${}_{\mathrm{I}}A$ form is prevented.

These steps are shown in Figure 38-12.

For a monotropic system, the metastable state can only change to the stable state; for an enantiotropic system, the transition point is critical for interconversion. Therefore, the formation temperature should be as far above the transition point as practical.

The ideal solution conditions to prevent ${}_{\mathrm{II}}A$ from converting to ${}_{\mathrm{I}}A$ are such that the solution phase, a, should be highly supersaturated, of a small volume, and in a relatively poor solvent. Rapid cooling is the method of choice for maintaining supersaturation with respect to ${}_{\mathrm{II}}A$. To help ensure that the rate of metastable crystallization is much greater than the rate of thermodynamic equilibration, small volumes and poor solvents for ${}_{\mathrm{I}}A$ are used. The use of dry ice for rapid

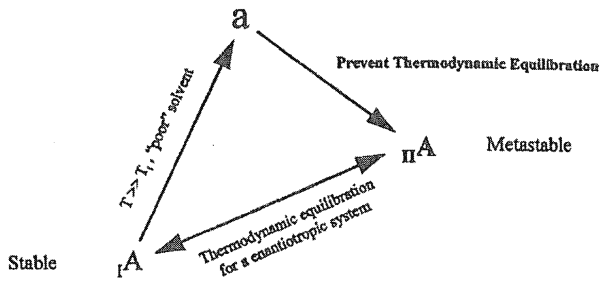
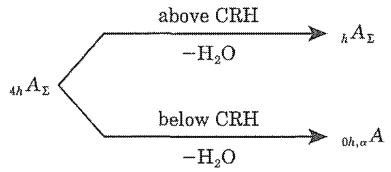


Figure 38-12. Formation of a metastable polymorph in a monotropic system.[14]

cooling with alcohol or acetone is common for these purposes. Once crystallization from the saturated solution phase, a, has occurred, it is important to filter and dry the precipitate as quickly as possible to prevent a fluid-phase transformation to the stable polymorph. Alternatively, if ${}_{\mathrm{I}}A$ can be melted without degradation, complete melting and rapid cooling of the melt is an another method of forming metastable forms. This avoids two major problems of solution-phase metastable polymorph formation—filtration and drying, both of which can promote interconversion.

Hydrate Stability: Importance of the Critical Relative Humidity —Relative humidity (RH) is the percentage of the maximum amount of moisture that air can hold. A substance is hygroscopic when it takes up this moisture from air. For a drug substance, the RH that is in equilibrium with a saturated aqueous solution of a solute is termed the critical relative humidity (CRH).[21] It is a key parameter that can influence the physical stability of solid-state hydrates. A number of studies have shown that the gain or loss of water from a hydrate can center on the CRH. Because water in organic crystals is never a passive entity (see *Hydrate Formation*, page 711), solid-state changes in the crystal are very likely to follow.

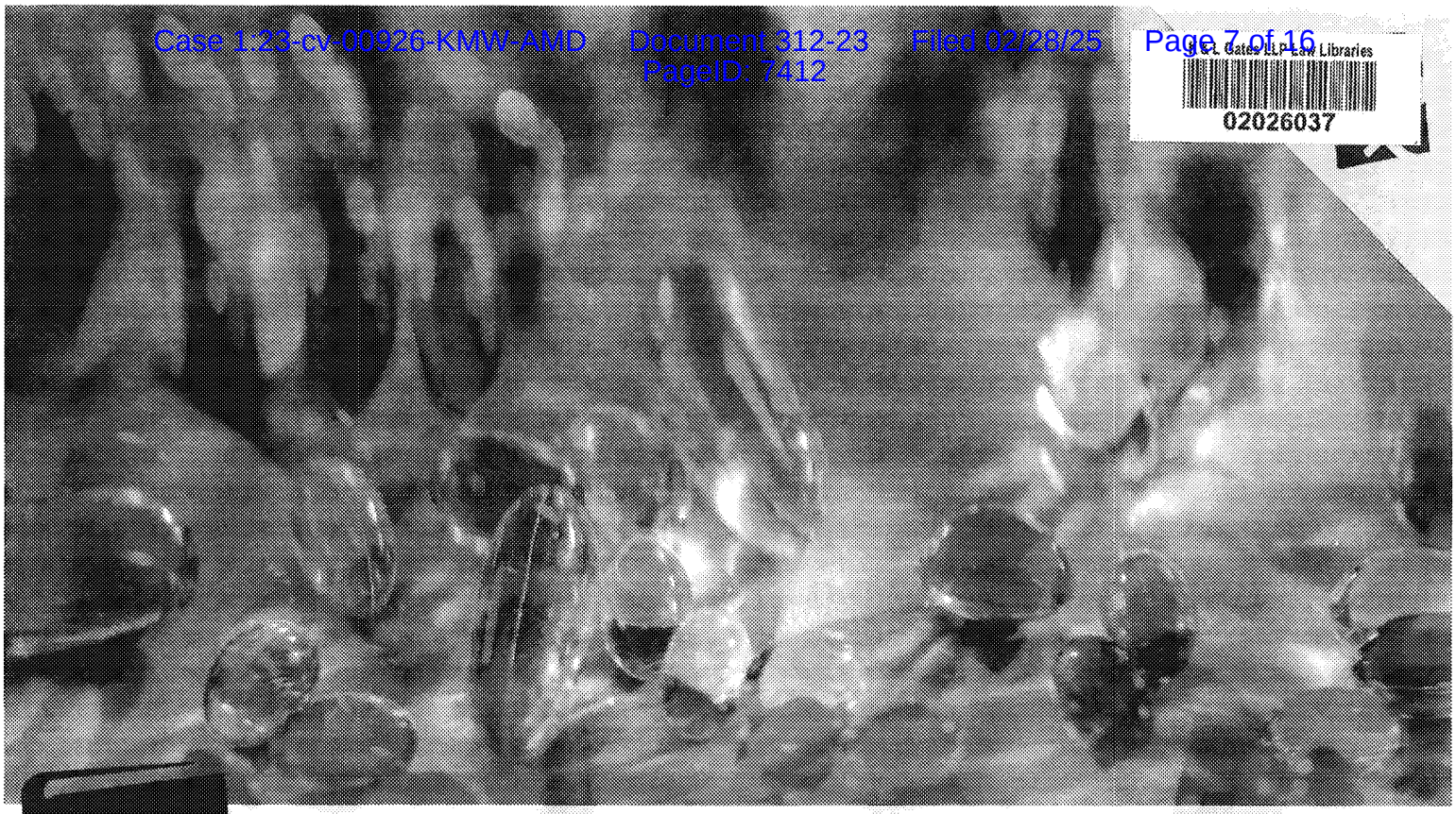
For the tetrahydrate sodium salt of a tetrazolate derivative, a number of different solid-state forms are possible.[22]



(29)

The conversion of ${}_{4h}A$ to ${}_{h}A$ requires elevated temperature and a RH above the CRH. Water's plasticizing action in reducing the intermolecular H-bonding between adjacent molecules is believed to be the mechanism that facilitates the solid-state transformation to the more stable ${}_{h}A$ crystal form.[23] Similarly, elevation of both temperature and RH were required to convert the ${}_{0h}A$ form of paroxetine HCl to the ${}_{0.5h}A$ form.[24] Water also promoted a solid-state transformation of the ${}_{\alpha}A$ form to the ${}_{0h}A$ form of a disodium leukotriene antagonist. The amorphous form initially picked up a small amount of water (2%) and then slowly released this water as the anhydrous form was formed. Conversely, the humidity-mediated conversion from ${}_{\mathrm{II}}A$ to ${}_{\alpha}A$ has been observed for another leukotriene antagonist.[25] Difficult hydrate situations have been dealt with by carefully defining the RH ranges of different species and setting specifications consistent with typical manufacturing environments.[26]

In general, hydrates that are more closely packed tend to be more physically stable with respect to moisture loss. The ideal solid state is one that is stable over a wide range of RH, such as the ${}_{0.5h}A$ form of paroxetine HCl.[24] For the sodium salt of the tetrazole derivative shown in Equations 29 and 30, the denser



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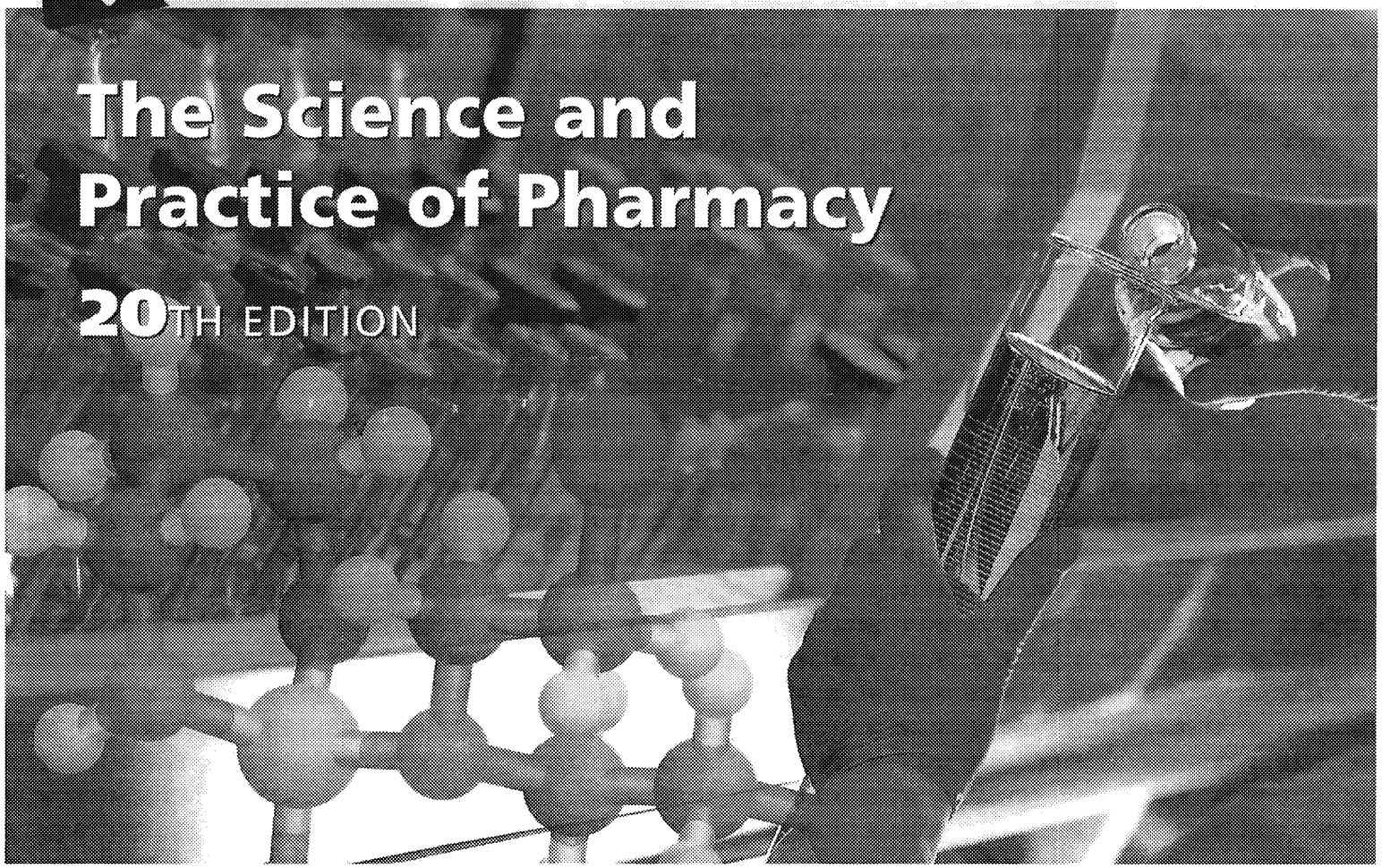

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CHAPTER 39

Solutions, Emulsions, Suspensions, and Extracts

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The dosage forms described in this chapter may be prepared by employing pharmaceutically and therapeutically acceptable vehicles. The active ingredient(s) may be dissolved in an aqueous or nonaqueous solvent or combination, by suspending the drug (if it is insoluble) in an appropriate medium, or by incorporating the medicinal agent into one of the two phases of an oil and water system. Such solutions, suspensions, and emulsions are further defined in subsequent paragraphs but some, with similar properties, are considered elsewhere in Remington.

These dosage forms are useful for a number of reasons. They can be formulated for different routes of administration: oral use, introduction into body cavities, or external application. The dose easily can be adjusted by dilution, and the oral liquid form can readily be administered to children or people unable to swallow tablets or capsules. Extracts eliminate the need to isolate the drug in pure form, allow several ingredients to be administered from a single source (eg, pancreatic extract), and permit the preliminary study of drugs from natural sources. Occasionally, solutions of drugs such as potassium chloride are used to minimize adverse effects in the gastrointestinal tract.

The preparation of these dosage forms involves several considerations on the part of the pharmacist, namely; purpose of the drug, internal or external use, concentration of the drug, selection of the liquid vehicle, physical and chemical stability of the drug and any excipients, preservation of the preparation, and use of appropriate excipients such as buffers, solubilizers, suspending agents, emulsifying agents, viscosity controlling agents, colors, and flavors. Oral preparations require that consideration be given to improving patient compliance by making an acceptable product; consequently, color, odor, and taste must be considered. These organoleptic factors are described in Chapter 55. The viscosity of a product also must be considered so that it has the proper palatability for an oral preparation and has the appropriate suspending properties if it is an emulsion or suspension. The theory pertaining to these systems is provided in Chapters 21 to 23. The theory of solutions, which involves solubility, ionization, pH control through the use of buffers, and solubilization, is discussed in Chapters 16 and 17. Because of the complexity of some manufactured products, compounding may be carried out with the aid of linear programming models to obtain the optimal product. Chapters 41 to 43 should be consulted for information on the preparation and characteristics of those liquid preparations that are intended for ophthalmic or parenteral use.

Much has been written during the past decade about the biopharmaceutical properties of, in particular, the solid dosage forms. In assessing the bioavailability of drugs in tablets and capsules, many researchers first have studied the absorption of drugs administered in solution. Because drugs are absorbed in their dissolved state, frequently it is found that the absorption rate of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablet or capsule. The bioavailability of a medicament, for oral ingestion and absorption, should be such that eventually all of the drug is absorbed as it passes through the gastrointestinal tract, regardless of the dosage form. Some formulation factors that may influence the bioavailability and pharmacokinetics of drugs in solution include concentration of the drug, volume of liquid administered, pH, buffer capacity, surface tension, specific gravity, viscosity, and excipients. Emulsions and suspensions are more complex systems and consequently the extent of absorption and pharmacokinetic parameters may be affected by a number of additional formulation factors such as; surfactants, type of viscosity agent, particle size and particle-size distribution, polymorphism, and solubility of drug in the oil phase. Specific examples are provided in Chapter 22.

There are a number of reasons for formulating drugs in forms in which the drug is not in the molecular state. These are improved stability, improved taste, low water solubility, palatability, and ease of administration. It becomes apparent then that each dosage form will have advantages and disadvantages.

Liquid preparations may be dispensed in one of three ways. The pharmacist may dispense the product in its original container, buy the product in bulk, and repackage it at the time a prescription is presented by the patient or compound the solution, suspension, or emulsion in the dispensary. Compounding may involve nothing more than mixing marketed products in the manner indicated on the prescription or, in specific instances, may require the incorporation of active ingredients and excipients in a logical and pharmaceutically acceptable manner into the aqueous or nonaqueous solvents that will form the bulk of the product.

The pharmacist, in the first instance, depends on the pharmaceutical manufacturer to produce a product that is effective, elegant, and stable when stored under reasonably adverse conditions. Most manufacturers attempt to guarantee efficacy by evaluating their products in a scientifically acceptable manner but, in some instances, such efficacy is relative. For example, cough mixtures marketed by two different manufacturers may contain the same active ingredients, and it becomes difficult to assess the relative merits of the two products. In such instances the commercial advantage gained by one over the other may be based on product acceptability and preference that includes such factors as color, odor, taste, pourability, uniformity, and packaging. Two additional important factors that must be considered in formulations are the stability of active and other ingredients, and the prevention of microbial contamination.

The stability of the active ingredient in the final product is of prime concern to the formulator. In general, drug substances are less stable in aqueous media than in the solid dosage form and it is important, therefore, to properly stabilize and preserve, in particular those solutions, suspensions, and emulsions that contain water. Certain simple chemical reactions can

appropriate preparation of aromatic waters is provided in *RPS-18*, Chapter 83, and RPS-17, Chapter 84.

The principal difficulty experienced in compounding prescriptions containing aromatic waters is due to a *salting out* action of certain ingredients, such as very soluble salts, on the volatile principle of the aromatic water. A replacement of part of the aromatic water with purified water is permissible when no other function is being served than that of a vehicle.

PRESERVATION

Aromatic waters will deteriorate with time and should, therefore, be made in small quantities, protected from intense light and excessive heat, and stored in airtight, light-resistant containers.

AQUEOUS ACIDS

The official inorganic acids and certain organic acids, although of minor significance as therapeutic agents, are of great importance in chemical and pharmaceutical manufacturing. This is especially true of acetic, hydrochloric, and nitric acids.

PERCENTAGE STRENGTHS

Many of the more important inorganic acids are available commercially in the form of concentrated aqueous solutions. The percentage strength varies from one acid to another and depends on the solubility and stability of the solute in water and on the manufacturing process. Thus, the official Hydrochloric Acid contains from 36.5 to 38.0% by weight of HCl, whereas Nitric Acid contains from 69 to 71% by weight of HNO_3.

Because the strengths of these concentrated acids are stated in terms of percent by weight, it is essential that specific gravities also be provided if one is to be able to calculate conveniently the amount of absolute acid contained in a unit volume of the solution as purchased. The mathematical relationship involved is given by the equation $M = V \times S \times F$, where M is the mass in g of absolute acid contained in V mL of solution having a specific gravity S and a fractional percentage strength F.

As an example, Hydrochloric Acid containing 36.93% by weight of HCl has a specific gravity of 1.1875. Therefore, the amount of pure HCl supplied by 100 mL of this solution is given by:

$$M = 100 \times 1.1875 \times 0.3693 = 43.85 \text{ g HCl}$$

INCOMPATIBILITIES

Although many of the reactions characteristic of acids offer opportunities for incompatibilities, only a few are of sufficient importance to require more than casual mention. Acids and acid salts decompose carbonates with liberation of carbon dioxide; in a closed container, sufficient pressure may be developed to produce an explosion. Inorganic acids react with salts of organic acids to produce the free organic acid and a salt of the inorganic acid. If insoluble, the organic acid will be precipitated. Thus, salicylic acid and benzoic acid are precipitated from solutions of salicylates and benzoates. Boric acid likewise is precipitated from concentrated solutions of borates. By a similar reaction, certain soluble organic compounds are converted into an insoluble form. Phenobarbital sodium, for example, is converted into phenobarbital that will precipitate in aqueous solution.

The ability of acids to combine with alkaloids and other organic compounds containing a basic nitrogen atom is used in preparing soluble salts of these substances.

It should be borne in mind that certain solutions, syrups, elixirs, and other pharmaceutical preparations, may contain free acid, which causes these preparations to exhibit the incompatibilities characteristic of the acid.

Acids also possess the incompatibilities of the anions that they contain and, in the case of organic acids, these are frequently of prime importance. These are discussed under the specific anions.

DILUTED ACIDS

The diluted acids in the USP are aqueous solutions of acids, of a suitable strength (usually 10% *w/v* but Diluted Acetic Acid is 6% *w/v*) for internal administration or for the manufacture of other preparations.

The strengths of the official undiluted acids are expressed as percentages in weight (*w/w*), whereas the strengths of the official diluted acids are expressed as percent in volume (*w/v*). It, therefore, becomes necessary to consider the specific gravities of the concentrated acids when calculating the volume required to make a given quantity of diluted acid. The following equation will give the number of milliliters required to make 1000 mL of diluted acid:

$$\frac{\text{Strength of diluted acid} \times 1000}{\text{Strength of undiluted acid} \times \text{sp gr of undiluted acid}}$$

Thus, if one wishes to make 1000 mL of Diluted Hydrochloric Acid USP using Hydrochloric Acid that assays 37.5% HCl (sp gr 1.18), the amount required is

$$\frac{10 \times 1000}{37.5 \times 1.18} = 226 \text{ mL}$$

Diluted Hydrochloric Acid USP has been used in the treatment of achlorhydria. However, it may irritate the mucous membrane of the mouth and attack the enamel of the teeth. The usual dose is 2 to 4 mL, well-diluted with water. In the treatment of achlorhydria no attempt is made to administer more than a relief-producing dose.

SOLUTIONS

A solution, in the present context, is a liquid preparation that contains one or more soluble chemical substances dissolved in water. The solute usually is nonvolatile. Solutions are used for the specific therapeutic effect of the solute, either internally or externally. Although the emphasis here is on the aqueous solution, certain preparations of this type such as syrups, infusions, and decoctions have distinctive characteristics and, therefore, are described later in the chapter.

Solvents, solubility and general methods for the incorporation of a solute in a solvent are discussed in Chapter 16. Solutions are usually bottled automatically with equipment of the type shown in Figure 39-1.

PREPARATION

A specific method of preparation is given in the compendia for most solutions. These procedures fall into three main categories.

Simple Solutions—Solutions of this type are prepared by dissolving the solute in most of the solvent, mixing until dissolved, then adding sufficient solvent to bring the solution up to the proper volume. The solvent may contain other ingredients that stabilize or solubilize the active ingredient. Calcium Hydroxide Topical Solution USP (Lime Water), Sodium Phosphates Oral Solution USP, and Strong Iodine Solution USP are examples.

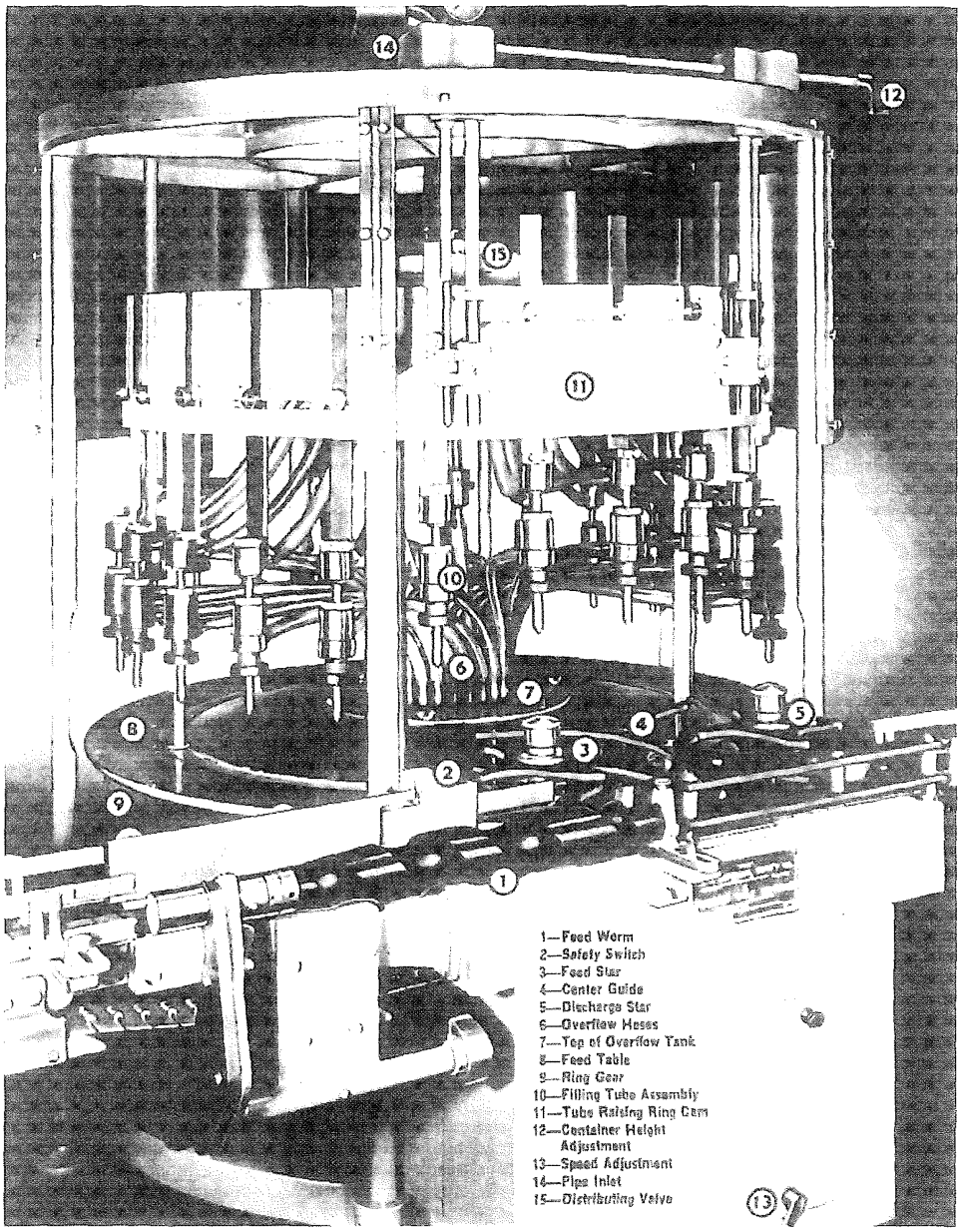

Figure 39-1. A rotary gravity bottle filler (courtesy, US Bottlers).

Calcium Hydroxide Topical Solution USP contains, in each 100 mL, not less than 140 mg of $Ca(OH)_2$. The solution is prepared by agitating vigorously 3 g of calcium hydroxide with 1000 mL of cool, purified water. Excess calcium hydroxide is allowed to settle out and the clear, supernatant liquid dispensed.

An increase in solvent temperature usually implies an increase in solute solubility. This rule does not apply, however, to the solubility of calcium hydroxide in water, which decreases with increasing temperature. The official solution is prepared at 25°.

Solutions containing hydroxides react with the carbon dioxide in the atmosphere.

$$OH^- + CO_2 \rightarrow HCO_3^-$$

$$OH^- + HCO_3^- \rightarrow CO_3^{2-} + H_2O$$

Calcium Hydroxide Topical Solution, therefore, should be preserved in well-filled, tight containers, at a temperature not exceeding 25°.

Strong Iodine Solution USP contains, in each 100 mL, 4.5 to 5.5 g of iodine, and 9.5 to 10.5 g of potassium iodide. It is prepared by dissolving 50 g of iodine in 100 mL of purified water containing 100 g of potassium iodide. Sufficient purified water then is added to make 1000 mL of solution. One g of iodine dissolves in 2950 mL of water. However, solutions of iodides dissolve large quantities of iodine. Strong Iodine Solution is, therefore, a solution of polyiodides in excess iodide.

$$I^- + nI_2 \rightarrow I^-_{(2n+1)}$$

Doubly charged anions may be found also.

$$2I^- + nI_2 \rightarrow I^{2-}_{(2n+2)}$$

Strong Iodine Solution is used in the treatment of iodide deficiency disorders such as endemic goiter.

Several antibiotics (eg, cloxacillin sodium, nafcillin sodium, and vancomycin), because they are relatively unstable in aqueous solution, are prepared by manufacturers as dry powders or granules in combination with suitable buffers, colors, diluents, dispersants, flavors and/or preservatives. These preparations, Cloxacillin Sodium for Oral Solution, Nafcillin for Oral Solution, and Vancomycin Hydrochloride for Oral Solution meet the requirements of the USP. Upon dispensing to the patient, the pharmacist adds the appropriate amount of water. The products are stable for up to 14 days when refrigerated. This period usually provides sufficient time for the patient to complete the administration of all the medication.

Solution by Chemical Reaction—These solutions are prepared by reacting two or more solutes with each other in a suitable solvent. An example is Aluminum Subacetate Topical Solution USP.

Aluminum sulfate (145 g) is dissolved in 600 mL of cold water. The solution is filtered, and precipitated calcium carbonate (70 g) is added, in several portions, with constant stirring. Acetic acid (160 mL) is added slowly and the mixture set aside for 24 hours. The product is filtered and the magma on the Buchner filter washed with cold water until the total filtrate measures 1000 mL.

The solution contains pentaquohydroxo- and tetraquodihydroxoaluminum(III) acetates and sulfates dissolved in an aqueous medium saturated with calcium sulfate. The solution contains a small amount of acetic acid. It may be stabilized by the addition of not more than 0.9% boric acid.

The reactions involved in the preparation of the solution are given below. The hexaquo aluminum cations first are converted to the nonirritating $[Al(H_2O)_5(OH)]^{2+}$ and $[Al(H_2O)_4(OH)_2]^{+}$ cations.

$$[Al(H_2O)_6]^{3+} + CO_3^{2-} \rightarrow [Al(H_2O)_5(OH)]^{2+} + HCO_3^-$$

$$[Al(H_2O)_6]^{3+} + HCO_3^- \rightarrow [Al(H_2O)_5(OH)]^{2+} + H_2O + CO_2$$

As the concentration of the hexaquo cations decreases, secondary reactions involving carbonate and bicarbonate occur.

$$[Al(H_2O)_5(OH)]^{2+} + CO_3^{2-} \rightarrow [Al(H_2O)_4(OH)_2]^{+} + HCO_3^-$$

$$[Al(H_2O)_5(OH)]^{2+} + HCO_3^- \rightarrow [Al(H_2O)_4(OH)_2]^{+} + H_2CO_3$$

The pH of the solution now favors the precipitation of dissolved calcium ions as the insoluble sulfate. Acetic acid now is added. The bicarbonate that is formed in the final stages of the procedure is removed as carbon dioxide.

Aluminum Subacetate Topical Solution is used in the preparation of Aluminum Acetate Topical Solution USP (Burow's Solution). The latter solution contains 15 mL of glacial acetic acid, 545 mL of Aluminum Subacetate Topical Solution and sufficient water to make 1000 mL. It is defined as a solution of aluminum acetate in approximately 5%, by weight, of acetic acid in water. It may be stabilized by the addition of not more than 0.6% boric acid.

Solution by Extraction—Drugs or pharmaceutical necessities of vegetable or animal origin often are extracted with water or with water containing other substances. Preparations of this type may be classified as solutions but, more often, are classified as extracts and are described at the end of this chapter.

DOUCHES

A douche is an aqueous solution directed against a part or into a cavity of the body. It functions as a cleansing or antiseptic agent. An *eye douche*, used to remove foreign particles and discharges from the eyes, is directed gently at an oblique angle and allowed to run from the inner to the outer corner of the eye. *Pharyngeal douches* are used to prepare the interior of the throat for an operation and cleanse it in suppurative conditions. Similarly, there are *nasal douches* and *vaginal douches*. Douches usually are directed to the appropriate body part by using bulb syringes (Chapter 109).

Douches most frequently are dispensed in the form of a powder with directions for dissolving in a specified quantity of water (usually warm). However, tablets for preparing solutions are available (eg, Dobell's Solution Tablets) or the solution may be prepared by the pharmacist. If powders or tablets are supplied, they must be free from insoluble material in order to produce a clear solution. Tablets are produced by the usual processes (see Chapter 45) but any lubricants or diluents used must be readily soluble in water. Boric acid may be used as a lubricant and sodium chloride normally is used as a diluent. Tablets deteriorate on exposure to moist air and should be stored in airtight containers.

Douches are not official as a class of preparations but several substances in the compendia frequently are employed as such in weak solutions; for example, benzalkonium chloride is used in various douches and Compound Sodium Borate Solution NFXI (Dobell's Solution) has been used as a nasal or pharyngeal douche. A sodium bicarbonate vaginal douche has been used to improve the postcoital test.

Vaginal douches are the most common type of douche and are used for cleansing the vagina and hygienic purposes. Liquid concentrates or powders, which may be prepared in bulk or as single-use packages, should be diluted or dissolved in the appropriate amount of warm water prior to use. The ingredients used in vaginal douches include antimicrobial agents such as benzalkonium chloride, the parabens or chlorothymol, anesthetics or antipruritics such as phenol or menthol. Astringents such as zinc sulfate or potassium alum, surface-active agents such as sodium lauryl sulfate, and chemicals to alter the pH such as sodium bicarbonate or citric acid also are used.

ENEMAS

Enema preparations are rectal injections employed to evacuate the bowel (evacuation enemas), influence the general system by absorption, or to affect a local disease. The latter two are called retention enemas. They may possess anthelmintic, nutritive, sedative, or stimulating properties, or they may contain radiopaque substances for roentgenographic examination of the lower bowel.

Sodium chloride, sodium bicarbonate, sodium monohydrogen phosphate, and sodium dihydrogen phosphate are used in enemas to evacuate the bowel. These substances may be used alone, in combination with each other, or in combination with irritants such as soap. Enema of Soap BPC 1963 is prepared by dissolving 50 g of soft soap in sufficient purified water to make 1000 mL of enema. Sodium Phosphates Enema USP contains 6 g of dibasic sodium phosphate heptahydrate and 16 g of monobasic sodium phosphate monohydrate in each 100 mL. Evacuation enemas usually are given at body temperature in quantities of 1 to 2 pt injected slowly with a syringe.

An official retention enema used for systemic purposes is aminophylline. Retention enemas are to be retained in the intestine and should not be used in larger quantities than 150 mL for an adult. Usually, the volume is considerably smaller, such as a few mL. *Microenema* is a term used to describe these small-volume preparations. Vehicles for retention microenemas have been formulated with small quantities of ethanol and propylene glycol, and no significant difference in irritation, as compared with water, was found. A number of other drugs such as valproic acid, indomethacin, and metronidazole have been formulated as microenemas for the purpose of absorption. The absorption of large-molecular-weight drugs, such as insulin, is under current investigation.

precipitates tragacanth, acacia, and agar from aqueous solutions. Similarly, it will precipitate many inorganic salts from similar solutions. The implication here is that such substances should be absent from the aqueous phase or present in such concentrations that there is no danger of precipitation on standing.

If an aqueous solution is added to an elixir, a partial precipitation of alcohol soluble ingredients may occur. This is due to the reduced alcoholic content of the final preparation. Usually, however, the alcoholic content of the mixture is not sufficiently decreased to cause separation. As vehicles for tinctures and fluidextracts, the elixirs generally cause a separation of extractive matter from these products due to a reduction of the alcoholic content.

Many of the incompatibilities between elixirs, and the substances combined with them, are due to the chemical characteristics of the elixir *per se,* or of the ingredients in the final preparation. Thus, certain elixirs are acid in reaction while others may be alkaline and will, therefore, behave accordingly.

GLYCERINS

Glycerins or glycerites are solutions or mixtures of medicinal substances in not less than 50% by weight of glycerin. Most of the glycerins are extremely viscous and some are of a jelly-like consistency. Few of them are used extensively. Glycerin is a valuable pharmaceutical solvent forming permanent and concentrated solutions not otherwise obtainable.

Glycerin is used as the sole solvent for the preparation of Antipyrine and Benzocaine Otic Solution USP. As noted under *Otic Solutions,* glycerin alone is used to aid in the removal of cerumen. Externol, a commercial product, contains 5% carbamide peroxide (urea hydrogen peroxide) in glycerin, has shown superior qualities in dispersing ear wax. A glycerin base was chosen as the optimum solvent for an otic preparation in a study involving the stability and antimicrobial activity of kanamycin sulfate otic drops.

Glycerins are hygroscopic and should be stored in tightly closed containers.

INHALATIONS AND INHALANTS

Inhalations

Inhalation preparations are so used or designed that the drug is carried into the respiratory tree of the patient. The vapor or mist reaches the affected area and gives prompt relief from the symptoms of bronchial and nasal congestion. The USP defines Inhalations in the following way:

> Inhalations are drugs or solutions or suspensions of one or more drug substances administered by the nasal or oral respiratory route for local or systemic effect. Solutions of drug substances in sterile water for inhalation or in sodium chloride inhalation solution may be nebulized by the use of inert gases. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles. Nebulized solutions may be breathed directly from the nebulizer, or the nebulizer may be attached to a plastic face mask, tent or intermittent positive pressure breathing (IPPB) machine.
>
> Another group of products, also known as metered-dose inhalers (MDIs) are propellant-driven drug suspensions or solutions in liquified-gas propellant with or without a cosolvent and are intended for delivering metered doses of the drug to the respiratory tract. An MDI contains multiple doses, often exceeding several hundred. The most common single-dose volumes delivered are from 25 to 100 μL (also expressed as mg) per actuation.
>
> Examples of MDIs containing drug solutions and suspensions in this pharmacopeia are Epinephrine Inhalation Aerosol and Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol, respectively.

Powders also may be administered by mechanical devices that require manually produced pressure or a deep inhalation by the patient, such as Cromolyn Sodium for Inhalation.

As stated in the USP, particle size is of major importance in the administration of this type of preparation. The various mechanical devices that are used in conjunction with inhalations are described in some detail in Chapter 109. It has been reported that the optimum particle size for penetration into the pulmonary cavity is of the order of 0.5 to 7.0 μm. Fine mists are produced by pressurized aerosols and hence possess basic advantages over the older nebulizers; in addition, metered aerosols deliver more uniform doses (see Chapter 50). A number of inhalations are described in the USP XXI; for example, Epinephrine Inhalation Solution is a solution of Epinephrine in Purified Water prepared with the aid of Hydrochloric Acid, and Isoproterenol Inhalation Solution is a solution of Isoproterenol Hydrochloride in Purified Water and may contain Sodium Chloride.

The term *inhalations*, defined by the BP, has a different meaning. These are solutions or suspensions of one or more active ingredients that may contain an inert, suspended diffusing agent. They are intended to release volatile constituents for inhalation, either when placed on a pad or when added to hot, but not boiling, water. Benzoin Inhalation BP contains benzoin, storax, and alcohol. The vapors from a preparation containing 1 teaspoonful of the tincture and 1 qt of boiling water may be inhaled. The device known as a vaporizer may be used with a number of commercially available preparations of this type (see Chapter 109).

Inhalants

The USP defines "inhalants" as follows:

> A special class of inhalations termed "inhalants" consists of drugs or combinations of drugs that, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant is administered is known as an inhaler.

Propylhexedrine Inhalant USP and Tuaminoheptane Inhalant USP XXII consist of cylindrical rolls of suitable fibrous material impregnated with propylhexedrine or tuaminoheptane (as carbonate), usually aromatized, and contained in a suitable inhaler. Propylhexedrine is the active ingredient in the widely used Benzedrex Inhaler. Both of these drugs are vasoconstrictors used to relieve nasal congestion. Inhalers that come in contact with the mouth or nasal passages become contaminated by bacteria, thus they should be restricted to personal use.

Another inhalant, Amyl Nitrite USP, is very flammable and should not be used where it may be ignited. It is packaged in sealed glass vials in a protective gauze. Upon breaking the vial, the gauze absorbs the drug that is then inhaled for the treatment of anginal pain (see page 1283).

LINIMENTS

Liniments are solutions or mixtures of various substances in oil, alcoholic solutions of soap, or emulsions and may contain suitable antimicrobial preservatives. These preparations that

For the most part, magmas and milks are intended for internal use, such as Milk of Magnesia USP and Dihydroxy Aluminum Aminoacetate Magma USP, although Bentonite Magma is used primarily as a suspending agent for insoluble substances for local application and occasionally for internal use. All magmas require a "Shake Well" label. Freezing must be avoided.

Several antimicrobial preservatives have been tested in liquid antacid preparations for their stability and effectiveness, such as benzoic acid, chlorhexidine, methylparaben, propylparaben, sorbic acid, propylene glycol, or ethanol. It was found that a combination of methylparaben and sorbic acid was superior to the parabens alone.

MIXTURES

The USP does not define the term mixture; however, the BP defines the term as the following:

> Mixtures are oral liquids containing one or more active ingredients, dissolved, suspended or dispersed in a suitable vehicle. Suspended solids may separate slowly on standing, but are easily redispersed on shaking.

The term mixture more commonly refers to a combination of two or more ingredients usually prepared by mechanical mixing. The insoluble substance usually does not make the mixture very viscous, and the particles may be held in suspension by using suitable suspending or thickening agents. This class was introduced originally to secure uniformity in the formulas of certain well-known and widely used preparations.

Frequently, the term *mixture* is applied loosely to aqueous preparations of every description. The term *shake mixture* is used often for liquid preparations that contain insoluble ingredients and, therefore, must be shaken before use. The term *suspension* is used to describe a number of similar preparations.

The following is a formula for a mixture in the BP, which is a solution for an extemporaneous preparation.

Ammonium Chloride Mixture

Ammonium Chloride	100 g
Aromatic Ammonia Solution	50 mL
Liquorice Liquid Extract	100 mL
Water, sufficient to produce	1000 mL

It should be prepared recently.

The following mixture is an example of a suspension and is used for the treatment of diarrhea. The pectin and the tragacanth in Kaolin Mixture with Pectin act as suspending agents. An alternate formula, based on Veegum (RT Vanderbilt) and sodium carboxymethylcellulose, has been proposed by Kalish.[42]

Kaolin Mixture with Pectin

Veegum	0.88 g
Sodium Carboxymethylcellulose	0.22 g
Purified Water	79.12 g
Kaolin	17.50 g
Pectin	0.44 g
Saccharin	0.09 g
Glycerin	1.75 g

Add the Veegum and the sodium carboxymethylcellulose to the water with continuous stirring. Add, with mixing, the kaolin. Mix the pectin, saccharin, and glycerin and add to the suspension. A preservative and flavoring agent may be added to the product.

The insoluble material in mixtures must be in a very finely divided state and uniformly distributed throughout the preparation. This is accomplished with colloid mills, special methods of precipitation, and suspending agents. There are three main reasons for having the insoluble substances in as fine a state of subdivision as possible.

1. The more nearly the colloidal state is approached by protectives, such as kaolin, magnesium trisilicate, or magnesium phosphate, the more active they become as adsorbents and protectives when in contact with inflamed surfaces.
2. Finely divided particles are suspended more readily and settle out much more slowly than large particles, thus enabling the patient to obtain uniform doses of suspended substances. Homogeneous mixtures are desirable, especially when administering medication to form an evenly distributed, protective coating on the gastrointestinal tract.
3. The palatability of many preparations is enhanced by the use of colloidal suspending agents.

Mixtures containing suspended material should have a *Shake Well* label affixed to the container in which they are dispensed.

Mixtures, including suspensions, are subject to contamination by microorganisms that remain viable and are a potential health hazard during the period of use of the products. Survival times of organisms depend on the preservative used. A kaolin pediatric mixture that contains benzoic acid kills organisms rapidly, whereas organisms survived for more than 1 week in a magnesium trisilicate mixture that contained no more than a trace of peppermint oil, as noted by Westwood.[43]

OFFICIAL SUSPENSIONS

The USP places particular emphasis on the term *suspension* by providing specific definitions for a variety of oral, parenteral, and ophthalmic preparations formulated in such a way that an insoluble substance is suspended in a liquid at some stage of the manufacturing or dispensing process. The USP definition begins as follows:

> Suspensions are liquid preparations that consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble. Dosage forms officially categorized as Suspensions are designated as such if they are not included in other more specific categories of suspensions, such as Oral Suspensions and Topical Suspensions (see these other categories). Some suspensions are prepared and ready for use, while others are prepared as solid mixtures intended for constitution just before use with an appropriate vehicle. Such products are designated *for Oral Suspension* . . .

This definition relates the term suspension to milks, magmas, and lotions that have been described above.

Although there are a number of monographs dealing with suspensions in the USP, neither the definition nor the monographs give specific directions for the preparation of the suspension, although pharmacopeias usually permit the addition of suitable flavoring agents, suspending agents, preservatives, and certified color additives. One procedure for the preparation of the commonly used Trisulfapyrimidines Oral Suspension is given below.

Trisulfapyrimidines Oral Suspension

Veegum	1.00 g
Syrup USP	90.60 g
Sodium Citrate	0.78 g
Sulfadiazine	2.54 g
Sulfamerazine	2.54 g
Sulfamethazine	2.54 g

Add the Veegum slowly and with continuous stirring to the syrup. Incorporate the sodium citrate into the Veegum–syrup mixture. Premix the sulfa drugs, add to the syrup, stir, and homogenize. Add sufficient 5% citric acid to adjust the pH of the product to 5.6. A preservative and a flavoring agent may be added to the product.

Methods of preparation for those formulations that contain several active ingredients and are produced in large quantities tend to be more complex than that given above and are described previously.

Many formulations for suspensions are given in the BP and the PC under *Mixtures*. A properly prepared suspension has a number of desirable properties:

1. The suspended material should not settle rapidly.
2. Particles that do settle should not form a hard cake and easily should be resuspended uniformly on shaking.
3. The suspension should pour freely from the container.

Insoluble powders that do not disperse evenly throughout the suspending medium when it is shaken should be powdered finely and levigated with a small amount of an agent such as glycerin, alcohol, or a portion of the dispersion of the suspending agent. The other ingredients are incorporated and the remainder of the dispersion of the suspending agent is incorporated gradually by trituration to produce the appropriate volume.

Suspensions intended for parenteral or ophthalmic use also are described in the USP. For a discussion of these suspensions, see Chapters 41 and 43.

EXTRACTION

Extraction, as the term is used pharmaceutically, involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by using selective solvents in standard extraction procedures.

The products so obtained from plants are relatively impure liquids, semisolids, or powders intended only for oral or external use. These include classes of preparations known as decoctions, infusions, fluidextracts, tinctures, pilular (semisolid) extracts, and powdered extracts. Such preparations popularly have been called galenicals, after Galen, the 2nd century Greek physician. For additional information concerning extraction and extractives, see RPS 15, Chapter 86.

Extraction continues to be of considerable interest in order to obtain improved yields of drugs derived from plant and animal sources. For example, improved extraction of digitalis glycosides has been carried out using a pulsating, perforated, bottom column. Other techniques include ultrasonics, rotary-film evaporators, liquid and supercritical carbon dioxide, hydrodistillation, liquid chromatography, multiple-solvent extraction, countercurrent extraction, and gravitation dynamics.

This discussion is concerned primarily with basic extraction procedures for crude drugs to obtain the therapeutically desirable portion and eliminate the inert material by treatment with a selective solvent, known as the menstruum. Extraction differs from solution in that the presence of insoluble matter is implied in the former process. The principal methods of extraction are maceration, percolation, digestion, infusion, and decoction. The quality of the finished product can be enhanced by standardizing primary extracts and carrying out analytical assays during production on the raw materials, intermediate products, and manufacturing procedures.

The processes of particular importance, insofar as the USP is concerned, are those of maceration and percolation, as described specifically for Belladonna Extract USP and Cascara Sagrada Extract USP. Most pharmacopeias refer to such processes for extraction of active principles from crude drugs. The USP provides general directions for both maceration and percolation under the heading of *Tinctures*.

Techniques of extraction methods continue to be investigated and applied to obtain higher yields of the active substance from natural sources, some of these methods include the use of different grinding and shearing techniques of plants, use of specific membranes for extraction, and different extraction procedures such as distillation, digestion, percolation, and microwaves. Some extraction methods are described.

Maceration—In this process the solid ingredients are placed in a stoppered container with 750 mL of the prescribed solvent and allowed to stand for a period of at least 3 days in a warm place with frequent agitation, until soluble matter is dissolved. The mixture is filtered and, after most of the liquid has drained, the residue on the filter is washed with sufficient quantity of the prescribed solvent or solvent mixture; the filtrates are combined to produce 1000 mL.

Percolation—The ground drug is mixed with the appropriate quantity of the prescribed solvent to make it evenly and uniformly damp. It is allowed to stand for 15 min, then transferred to a percolator (a narrow coned-shaped vessel, open at both ends) and packed. Sufficient prescribed solvent is added to saturate the drug. The top is placed on the percolator, and when the liquid is about to drip from the apparatus, the lower opening is closed. The drug is allowed to macerate for 24 hours or for the specified time. If no assay is directed, the percolation is allowed to proceed slowly or at the specified rate gradually adding sufficient solvent to produce 1000 mL of solution. If an assay is required, only 950 mL of percolate are collected and mixed and a portion assayed as directed. The rest of the percolate is diluted with the solvent to produce a solution that conforms to the required standard and then mixed.

Digestion—This is a form of maceration in which gentle heat is used during the process of extraction. It is used when moderately elevated temperature is not objectionable and the solvent efficiency of the menstruum is increased thereby.

Infusion—An infusion is a dilute solution of the readily soluble constituents of crude drugs. Fresh infusions are prepared by macerating the drugs for a short period of time with either cold or boiling water. US official compendia have not included infusions for some time. An example is Concentrated Compound Gentian Infusion BP 1973.

Decoction—This once-popular process extracts water-soluble and heat-stable constituents from crude drugs by boiling in water for 15 min, cooling, straining, and passing sufficient cold water through the drug to produce the required volume.

EXTRACTIVE PREPARATIONS

After a solution of the active constituents of a crude drug is obtained by maceration or percolation, it may be ready for use as a medicinal agent, as with certain tinctures or fluidextracts, or it may be processed further to produce a solid or semisolid extract.

For a discussion of resins and oleoresins obtained by solvent extraction of plant exudates see Chapter 26, under *Plant Exudates*.

TINCTURES

Tinctures are defined in the USP as being alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances, an example of the latter being Iodine Tincture. Traditionally, tinctures of potent vegetable drugs essentially represent the activity of 10 g of the drug in each 100 mL of tincture, the potency being adjusted following assay. Most other tinctures of vegetable drugs represent the extractive from 20 g of the drug in 100 mL of tincture.